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# Chronopharmacokinetics of nicotine

*Rationale:* For high-clearance drugs such as nicotine, hemodynamic changes throughout the day may be expected to influence the rate of metabolism.

*Material and methods:* To assess the effects of meals and diurnal rhythms on nicotine clearance, an intravenous infusion of nicotine bitartrate was administered for 48 hours to 11 subjects. Two models to determine nicotine clearance variation throughout the day are described. Both models were used to estimate the mean effect of meal and diurnal rhythms on nicotine clearance and individual parameters that were regressed against baseline covariates. Clearance was modeled as a function of time [CL(t)] and split it in three components: a (constant) baseline value ($\theta_1$), its circadian (diurnal) variation, and the effect of meal: CL(t) = [$\theta_1$ + circadian(t)] [1 + meal(t)]. A two-compartmental (time-variant) model incorporating CL(t) was then fitted to the data providing estimates of CL(t) conditional on literature values of the time-invariant parameters (volume of distribution and intercompartmental clearances).

*Results:* The estimated circadian(t) showed a maximum at approximately 11 AM and a flat minimum from 6 PM to 3 AM; the estimated meal(t) showed a sharp increase up to 1 hour (after the meal), at which point clearance is increased 42%, and a slower decrease thereafter, returning to baseline (zero) after 2.8 hours. Individual estimates of baseline clearance are found to have a linear relationship with body weight. No other covariate, sex in particular, effect could be found. (Clin Pharmacol Ther 1996;60:385-95.)

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Smokers tend to regulate the intake of nicotine, adjusting their smoking behavior to maintain a certain concentration of nicotine in the body.[1] Conversely, levels of nicotine in the body may influence when a person smokes a cigarette, how much nicotine he or she inhales from the cigarette, or both. The level of nicotine in the body is determined by the dose taken in and the rate of elimination. Nicotine is eliminated primarily by hepatic metabolism by way of C-oxidation to cotinine.[2] Nicotine is metabolized rapidly, so that the hepatic extraction indicates that the clearance of nicotine is likely to be dependent on liver blood flow.

Changes in drug metabolism throughout the day have been described for various drugs.[3-5] For high-clearance drugs such as nicotine, hemodynamic changes throughout the day may be expected to influence the rate of metabolism. For example, eating a meal increases liver blood flow and may increase drug clearance. We have shown previously that eating a meal lowers blood nicotine concentrations,[6] consistent with an increase in clearance. Cardiac output and liver blood flow vary throughout the day as a function of activity with a decline during sleep.[7] It might be expected that nicotine clearance would decline overnight as a function of reduced liver blood flow. Consistent with this hypothesis is the observation that during constant intravenous infusion of nicotine for 24 hours, there is a progressive increase in plasma nicotine concentrations throughout the night[8] despite half-life values after brief infusions of 2 to 3 hours. This observation suggests the possibility that nicotine clearance is reduced overnight compared with that during the day.

This study aims to characterize the chronopharmacokinetics of nicotine in people. A 48-hour con-

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tinuous intravenous infusion was administered to examine blood levels of nicotine throughout the day under steady-state dosing conditions. Resultant pharmacokinetic data were modeled to determine the effects of meals and circadian influences on the clearance of nicotine.

## METHODS

***Subjects.*** Eleven healthy subjects (six men and five women) who were 23 to 54 years of age and who smoked 20 or more cigarettes per day were studied. They ranged in weight from 57.5 to 94.0 kg (mean 70.4 kg) and in height from 155 to 182 cm (mean 171.5 cm). Five (45%) subjects were white, four (36%) were black, and two (19%) were Asian. Two additional subjects dropped out of the study because they could not abstain from smoking for 48 hours. Baseline covariates (age, sex, weight, height, and race) were recorded for the pharmacokinetics analysis. All subjects gave written consent after being advised of the nature of the risks of the study. The subjects were confirmed to be in good health by physical examination, medical history, and clinical laboratory tests. Subjects were admitted to the General Clinical Research Center at the San Francisco General Hospital for 5 days, during which time smoking was not permitted. Compliance with nonsmoking was assessed by periodic measurements of expired carbon monoxide concentrations. Meals were administered at fixed times each day for all subjects. Breakfast was given at 8 AM, lunch at 12 noon, and dinner at 5 PM. Caffeine-containing beverages were prohibited.

***Experimental protocol.*** After a washout period of 3 days, an intravenous infusion of nicotine bitartrate (1.25 mg base/hr) starting at 8 AM was initiated and continued for 48 hours. One catheter on one arm was used for infusion, and another catheter on the other arm was used for blood sampling. Blood samples were taken for measurement of nicotine concentrations before infusion was performed, every 2 hours for the next 22 hours (until 6 AM), then every hour for the next 20 hours (until 2 AM), and then every 2 hours for the remaining 6 hours (ending at 6 AM). In addition, a sample was taken 30 minutes after each mean was begun (i.e., 8:30 AM, 12:30 PM, and 5:30 PM) to better characterize the kinetics related to meals.

Concentrations of nicotine were measured by gas liquid chromatography with nitrogen-phosphorus detection as described by Jacob et al.[9] and modified for the use of a capillary column.

***Data analysis.*** Generally nicotine concentration kinetics are well described by a biexponential function,[8] which can be written (in differential form) as follows:

$$\frac{dA_1(t)}{dt} = -\left(\frac{CL}{V_C} + \frac{Q}{V_C}\right) A_1(t) + \frac{Q}{V_{SS} - V_C} A_2(t) \qquad (1a)$$

$$\frac{dA_2(t)}{dt} = \frac{Q}{V_C} A_1(t) - \frac{Q}{V_{SS} - V_C} A_2(t) \qquad (1b)$$

in which $A_1$ and $A_2$ are the amount of nicotine in the central and peripheral compartment, respectively, $V_C$ is the volume of the central compartment, $V_{SS}$ is the volume at steady state, Q is the intercompartmental clearance [$Q = k_{21}(V_{SS} - V_C)$, where $k_{21}$ is the elimination constant from compartment 2 to compartment 1], and CL the constant clearance of nicotine from the central compartment. In this article we modeled clearance as a function of time (CL(t)) and split it in three components: a baseline value, the circadian (diurnal) variation, and the effect of meal. The model used for clearance can be written as follows:

$$CL(t) = [\theta_1 + \text{circadian}(t)][1 + \text{meal}(t)] \qquad (2)$$

in which $\theta_1$ represents the baseline component, circadian(t) the diurnal variation of clearance, and meal(t) the fraction of increase in clearance caused by the meal. Substituting CL(t) for CL in equation 1a obtains a time-variant (versus time-invariant) two-compartment model, which will turn out to be more appropriate to describe nicotine kinetics.

Mostly to compare across two possible approaches, we developed two different models: a semiparametric and a parametric one. For the parametric model:

$$\text{circadian}(t) = \theta_2 \sin\left(\frac{2\pi}{\omega}(t + \theta_3)\right) \qquad (3)$$

in which $\omega$, the period of the circadian component of clearance, was fixed to 24 hours, and $\theta_2$ (amplitude) and $\theta_3$ (phase) were estimated from the data. The effect of meal is given by the following:

$$\text{meal}(t) = \begin{cases} \sum_k \frac{\theta_6\theta_4}{\theta_4 - \theta_5}\left(e^{-\theta_5(t-t_k)} - e^{-\theta_4(t-t_k)}\right) & \text{if } t > t_k \\ 0 & \text{otherwise} \end{cases} \qquad (4)$$

in which $t_k$ indicates the time of the k-th meal, and $\theta_4$, $\theta_5$, and $\theta_6$ are model-specific parameters (in this case a Bateman function).

For the semiparametric model we used nonparametric functions (splines instead of the cosine and

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exponential functions), but maintained a parametric two-compartmental structure. Splines are flexible functions that are basically piecewise polynomials which join at certain locations called breakpoints ($\zeta$) and match their derivatives up to the degree minus one of the polynomials. For example, a linear spline matches only the values of the polynomials at the breakpoints to give the somewhat familiar "broken line." We used cubic splines in this article.

For the circadian component we used a periodic cubic spline; this matches all derivatives at boundaries of the period (in this case 0 and 24 hours) in the same way as the cosine function used previously. The number of free parameters in a periodic spline equals the number of its breakpoints minus 2. For meal(t) we used the following:

$$\text{meal}(t) = \begin{cases} \sum_k s(t - t_k) & \text{if } t > t_k \\ 0 & \text{otherwise} \end{cases} \quad (5)$$

in which s(t) indicates a so-called natural cubic spline (this has second derivatives at the first and last breakpoint equal to zero). To make s(t) a meaningful model for the meal effect, we constrained it to be positive and equal to zero at the time of meal and at the last breakpoint. The position (in time) of the last breakpoint of the spline is one of the parameters to be estimated; it characterizes the duration of the meal effect because s(t) reaches zero at this time and thereafter. The number of free parameters in the meal effect spline equals the number of breakpoints minus one.

For both splines the first breakpoint was positioned at zero, and the other breakpoints were equispaced between the first and the last ones (at 24 hours and at the estimated end of meal effect for the periodic and natural spline, respectively). To determine how many breakpoints to use (increasing breakpoints increases the number of parameters in the splines and therefore their flexibility) we tried all combinations from two to six breakpoints and determined the best combination with the Akaike information criterion.[10] (This criterion requires a decrease of the objective function of at least two points per additional parameter for selecting the larger over the smaller model.)

In a first stage we fit $A_1/V_c$ as given by equation (1) (with CL(t) replacing the constant CL) to the pooled data from all individuals to estimate circadian(t), meal(t), and $\theta_1$, fixing $V_C$, $V_{SS}$, and Q to literature values (see Benowitz et al.[8] and following text). This was done for the two time-varying clearance models, parametric and semiparametric.

In a second stage to characterize interindividual variability we fit the following model to each individual's data:

$$\text{circadian}_j(t) = \gamma_{1j}\widehat{\text{circadian}}\,(t + \gamma_{2j}) \quad (6)$$

where j indicates the j-th individual, and $\widehat{\text{circadian}}$ (t) is the estimate obtained at step 1. This model states that individuals differ in the amplitude of circadian effect and in, for example, the time of maximum effect that is changed by the time shift $\gamma_{2j}$. For the meal effect we used:

$$\text{meal}_j(t) = \gamma_{3j}\widehat{\text{meal}}(t,\gamma_{4j}\zeta) \quad (7)$$

where $\widehat{\text{meal}}(t)$ is the estimate obtained at step 1, and $\zeta$ indicates the breakpoints of the meal spline. Multiplying the breakpoints by $\gamma_{4j}$ has the effect of scaling the function on the time axis; this allows a different time of maximum effect and of end of effect. Finally, individuals' estimates of baseline clearance ($\gamma_{5j}$) were allowed. Models of this sort (often referred to as "template models," where, e.g., $\widehat{\text{meal}}(t)$ is the template that can be scaled and shifted in time to characterize individuals) are often used in the literature.[11,12] The total number of parameters to be estimated for each individual is five.

From $\widehat{\text{circadian}}(t)$, $\widehat{\text{meal}}(t)$, and the individual estimates of $\gamma_{ij}$, $i = 1, \ldots, 5$, we computed the more intuitively meaningful parameters: (1) $T_{max,j}$, the time of the maximum effect of meal, (2) $M_{max,j}$, the maximum effect of meal, (3) $T_{99,j}$, the time, after $T_{max,j}$, at which 1% of maximum effect is present, (4) $A_{max,j}$, the maximum of $\widehat{\text{circadian}}_j(t)$, and (5) $A_{min,j}$, the minimum of $\widehat{\text{circadian}}_j(t)$, which we will report, together with the individual estimates of baseline clearance, to express interindividual differences.

To determine whether the measured covariates (sex, race, age, weight, and height) influence these estimated parameters, we used a Wilcoxon test for sex, Kruskal-Wallis for race, and linear regression for continuous covariates effect (weight, age, and height). The computer software NONMEM[13] was used to estimate the parameters. We used a proportional error model for all fits.

## RESULTS

Fig. 1 shows the fit of the data to a two-compartment model with $V_C$ = 63.8 L, $V_{SS}$ = 212.6 1, Q = 183.1 L/hr, and a constant clearance of 71.6 L/hr, as reported by Benowitz et al.[8]

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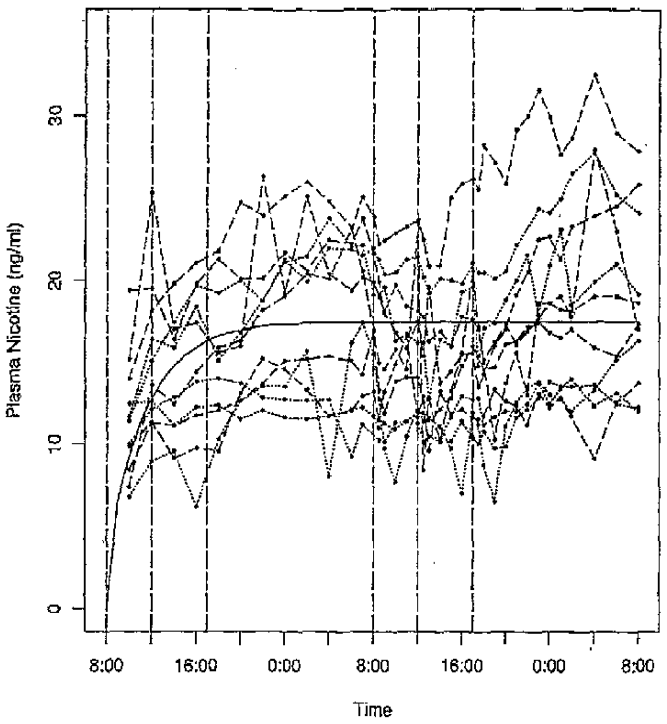


**Fig. 1.** Two-compartment body model fit to data versus clock time. The *solid line* is the prediction. The *dots* are the observed concentrations for individual subjects. The *dashed lines* connecting the *dots* are for the male subjects, and the *dotted* lines are for the females. The *vertical long dashed lines* are the meal starting times.

***Semiparametric model.*** The fit of the semiparametric model is shown in Fig. 2. There is a substantial improvement of the fit to the data compared with the two-compartment model with constant clearance (shown in Fig. 1) as assessed either by the objective function (which drops from 1682 to 1533) or by visual inspection. (Note that a drop of 14 points would be sufficient to prefer the semiparametric model.) The circadian spline requires four coefficients (six breakpoints) and showed a maximum at approximately 11 AM and a flat minimum from 6 PM to 3 AM (Fig. 3, *A, solid line*). Similar results were obtained with three and five coefficients, although in both cases the flat region is substituted by a single minimum (not shown). The spline describing the meal effect requires three coefficients. The meal effect lasted for 2.8 hours with a sharp increase up to 1.1 hour and a slower decrease thereafter. Fig. 3, *B* shows the pooled estimate of meal effect *(solid line)* and the individuals' estimates *(dotted lines)*. The maximum effect of a meal was estimated to be a 42% increase in clearance. Fig. 3, *C* shows the pooled estimate of clearance versus time over the 2 days of the experiment *(solid line)* and the envelope including the prediction of all individuals *(dashed line)*. (We do not show individuals' estimates because the graph is too cluttered.) The effect of meal seems to be the most important component of clearance, either when we look at the plot of clearance versus time or when we consider the drops in objective function when we include one component of clearance at a time.

Individual estimates of the parameters $T_{max,j}$, $M_{max,j}$, $T_{99,j}$, $A_{max,j}$, $A_{min,j}$, and $\gamma_{5,j}$ are reported in Table I. The coefficient of variation of the baseline clearance is approximately 28%, similar to what has been previously reported.[8] The other parameters exhibit a higher variability: coefficient of variation of 35% for $T_{max}$ and $T_{last}$, 45% for $A_{min}$ and $A_{max}$, and 66% for $M_{max}$. The mean estimates corresponding

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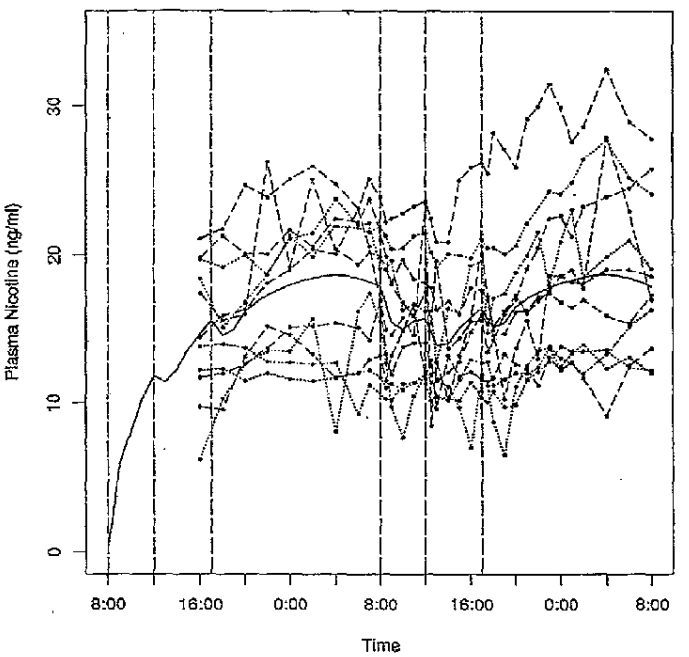


**Fig. 2.** Semiparametric fit of data. See *legend* to Fig. 1.

to the meal effect are physiologically reasonable; the maximum increase in clearance is obtained 1 hour after the beginning of a meal, and the meal effect lasts 2.7 hours. Fig. 4 shows the predictions for each subject with their estimated parameters. Note the overall good fit to the data (which might be made better with a more flexible individuals' model) and the high variability in the shape of the individual responses.

***Parametric model.*** The fit of the parametric time-varying clearance model shows the same (significant) improvement compared with the (time-invariant) two-compartment fit.

Individual estimates of the parameters $T_{max,j}$, $M_{max,j}$, $T_{99,j}$, $A_{max,j}$, $A_{min,j}$ (which equals $-A_{max,j}$), and $\gamma_{5,j}$ are reported in Table II. The main characteristics of the parametric estimate of the circadian component are similar to those of the semiparametric estimate; the peak clearance is obtained at approximately 10 AM, and the maximum decrease in the circadian clearance are of the same absolute value (7.4 L/hr for the parametric model versus 6.4 L/hr for the semiparametric). The major differences between the two estimates of circadian component are that (1) the parametric estimate is symmetric around the baseline clearance, which is not the case for the semiparametric one, and (2) the parametric estimate does (can) not show the flat portion of the circadian component seen in the selected semiparametric estimate.

The parametric estimate of the meal effect differs to a greater extent from the semiparametric estimate; the estimated clearance function is very sharp, with a maximum at 10 minutes and a slower decrease. The effect of meal at 2½ hours after the meal is, however, almost identical: 4.1% and 3.5% for the semiparametric and parametric models, respectively.

Computing the individual parameters with the parametric model leads to somewhat different results (Table II). The most important differences are for the mean baseline clearance (68 L/hr for the parametric model versus 76 L/hr for the semiparametric) and the effect of meal (69.6% maximum increase in clearance for the parametric model versus 51.1% for the semiparametric). Sometimes the parametric model estimates $T_{max}$ close to the time

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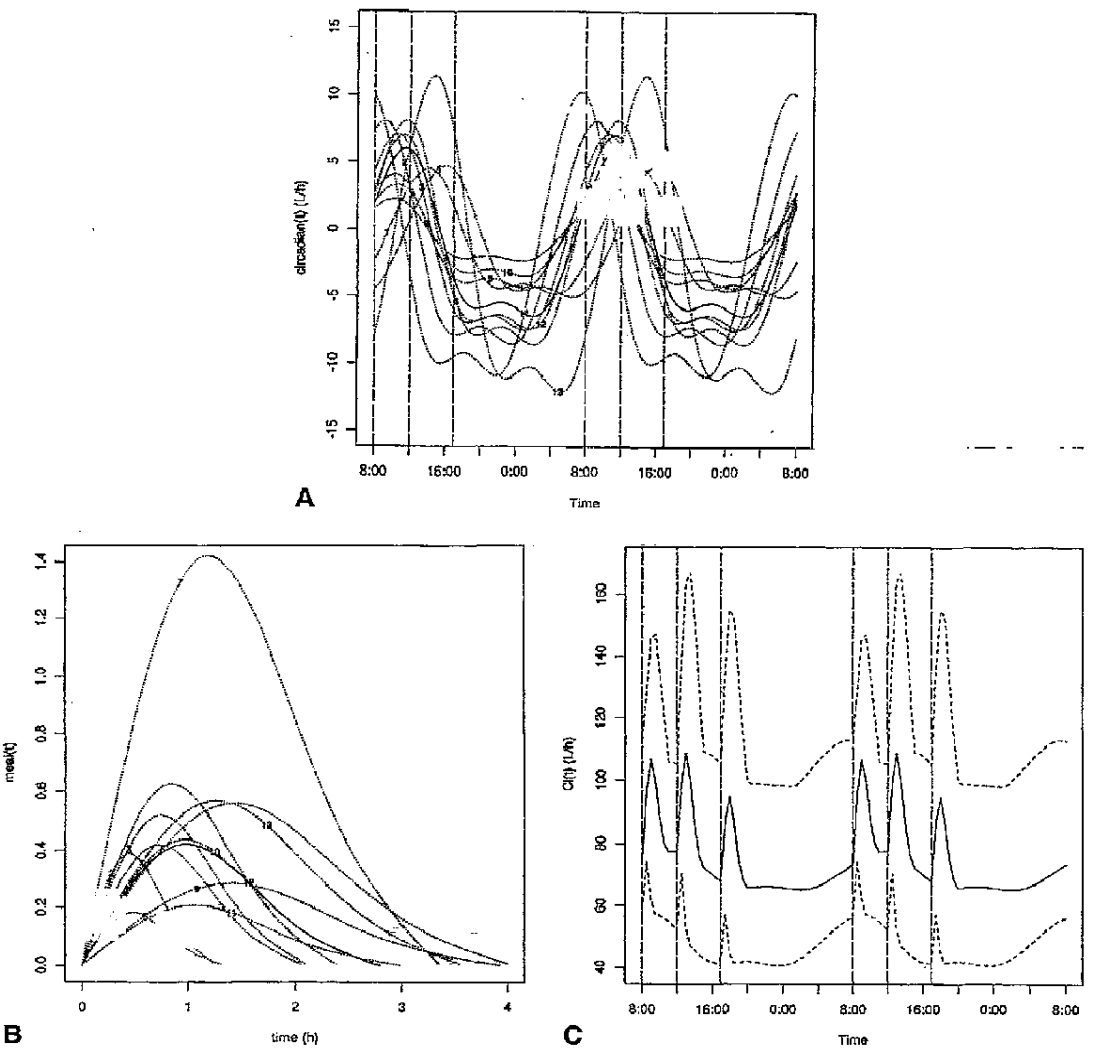


**Fig. 3. A,** Estimated circadian component of clearance [circadian(t)] versus clock time. The *solid line* is the pooled data estimate, and the *dotted lines* are the individuals' curves. **B,** Estimated meal effect on clearance [meal(t)] versus time (in hours). Meal effect is expressed as a fractional increase. The *solid line* is the pooled data estimate, the *dotted lines* the individuals' curves. **C,** Estimated resulting total clearance [CL(t)] versus clock time. The *solid line* is the pooled data estimate, the *dashed line* is the envelope including all individuals' predictions. The *vertical long dashed lines* are the meal starting times. Estimates are based on the semiparametric model.

of meal (particularly in subjects 2 and 9). The reason for this apparent lack of practical identifiability of $T_{max}$ (compare with the estimates obtained by the semiparametric model) is probably due to the sampling design (the first observation is half an hour after the meal). The estimates of $T_{99,j}$ indicate a too-large persistence of meal effect (the mean is 9.46 hours), which is one of the reasons to reject the

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**Table I.** Individual parameter estimates (semiparametric model)

| *Subject No.* | $\gamma_{5,j}$ *(L/hr)* | $T_{max,j}$ *(hr)* | $M_{max,j}$ | $T_{99,j}$ *(hr)* | $A_{min,j}$ *(L/hr)* | $A_{max,j}$ *(L/hr)* |
|---|---|---|---|---|---|---|
| 1 | 65.6* | 0.735 | 0.421 | 2.06 | −4.81 | 4.53 |
| 2 | 49.2 | 0.452 | 0.391 | 1.26 | −8.6 | 8.1 |
| 3 | 81.7 | 0.753 | 0.518 | 2.11 | −7.56 | 7.12 |
| 5 | 99.9 | 0.483 | 0.185 | 1.35 | −5.02 | 4.72 |
| 6 | 59.3 | 1.44 | 0.559 | 4.02 | −8.63 | 8.13 |
| 7 | 59.3 | 1.19 | 1.42 | 3.34 | −2.41 | 2.27 |
| 9 | 102 | 1.39 | 0.284 | 3.90 | −4.36 | 4.1 |
| 10 | 54.3 | 0.977* | 0.438* | 2.73* | −3.53 | 3.32 |
| 11 | 103 | 1.07 | 0.208 | 2.98 | −10.9 | 10.3 |
| 12 | 63.1 | 0.852 | 0.625 | 2.38 | −7.47* | 7.04* |
| 13 | 98.1 | 1.27 | 0.567 | 3.56 | −12.1 | 11.4 |
| Mean | 76.0 | 0.965 | 0.511 | 2.70 | −6.85 | 6.45 |
| SD | 21.3 | 0.342 | 0.336 | 0.957 | 3.09 | 2.91 |

$\gamma_{5,j}$, The baseline individual clearance; $T_{max,j}$, the time from beginning of meal to the maximal postmeal change in clearance, $M_{max,j}$, the maximum change in clearance caused by the effects of the meal; $T_{99,j}$, the time, after $T_{max,j}$, at which 1% of the individual meal effect is left; $A_{min,j}$, the maximum circadian decrease in clearance below the baseline clearance; $A_{max,j}$, the maximum circadian increase in clearance above the baseline clearance.
*Median value for each parameter.

parametric model in favor of the semiparametric one.

In terms of goodness of fit the semiparametric and the parametric model give similar results. The objective function for the pooled fits is 1533.4 for the semiparametric model and 1534.5 for the parametric model. For the individuals' fits the square root of the mean squared differences between individuals' data and predictions is 0.106 for the semiparametric model and 0.107 for the parametric model.

***Covariates effects.*** Individual estimates of baseline clearance are found to have a linear relationship with body weight (slope = 1.369; $p = 0.006$). No other covariates were found to be related with the estimated parameters. In particular, there is no sex-related difference either on the diurnal variation in clearance or in the effect of meals.

## DISCUSSION

Our study is novel in two aspects. First, we provide new information on the human biologic characteristics of nicotine. Second, we present an innovative modeling technique for studying meal and circadian influences on drug clearance.

We have previously reported that eating a meal while receiving a continuous intravenous infusion of nicotine results in a lowering of plasma nicotine concentrations.[6] This observation is consistent with increased clearance caused by an increase in hepatic blood flow, which is known to occur after eating.[14] In our earlier work we reported a change in nicotine clearance but made no attempt to quantitate the magnitude of change and duration of change in clearance. The observation of a progressive increase in plasma nicotine concentrations overnight during a 24-hour intravenous infusion of nicotine suggested a decline in nicotine clearance overnight, but the change in clearance was not quantitated.[8]

This study was designed specifically to quantitate the temporal changes in nicotine clearance throughout the day with a particular emphasis on changes that occur with meals and at night. A 48-hour infusion was used to distinguish the accumulation of nicotine overnight caused by a long terminal half-life versus an actual change in clearance. Meals were administered at fixed times of day, and nicotine blood concentrations were sampled frequently after meals to be able to characterize the details of the meal effect on nicotine kinetics.

The modeling techniques we use are to the best of our knowledge unique. We not only use nonparametric functions to represent diurnal variation, but we also incorporate the additional feature of modeling the effects of discrete events (meals), which appears to be previously unreported in the literature. More standard modeling of circadian variation is generally limited to the use of cosine functions.

The use of splines with different numbers of breakpoints as nonparametric functions and the Akaike criterion to choose the number of break-

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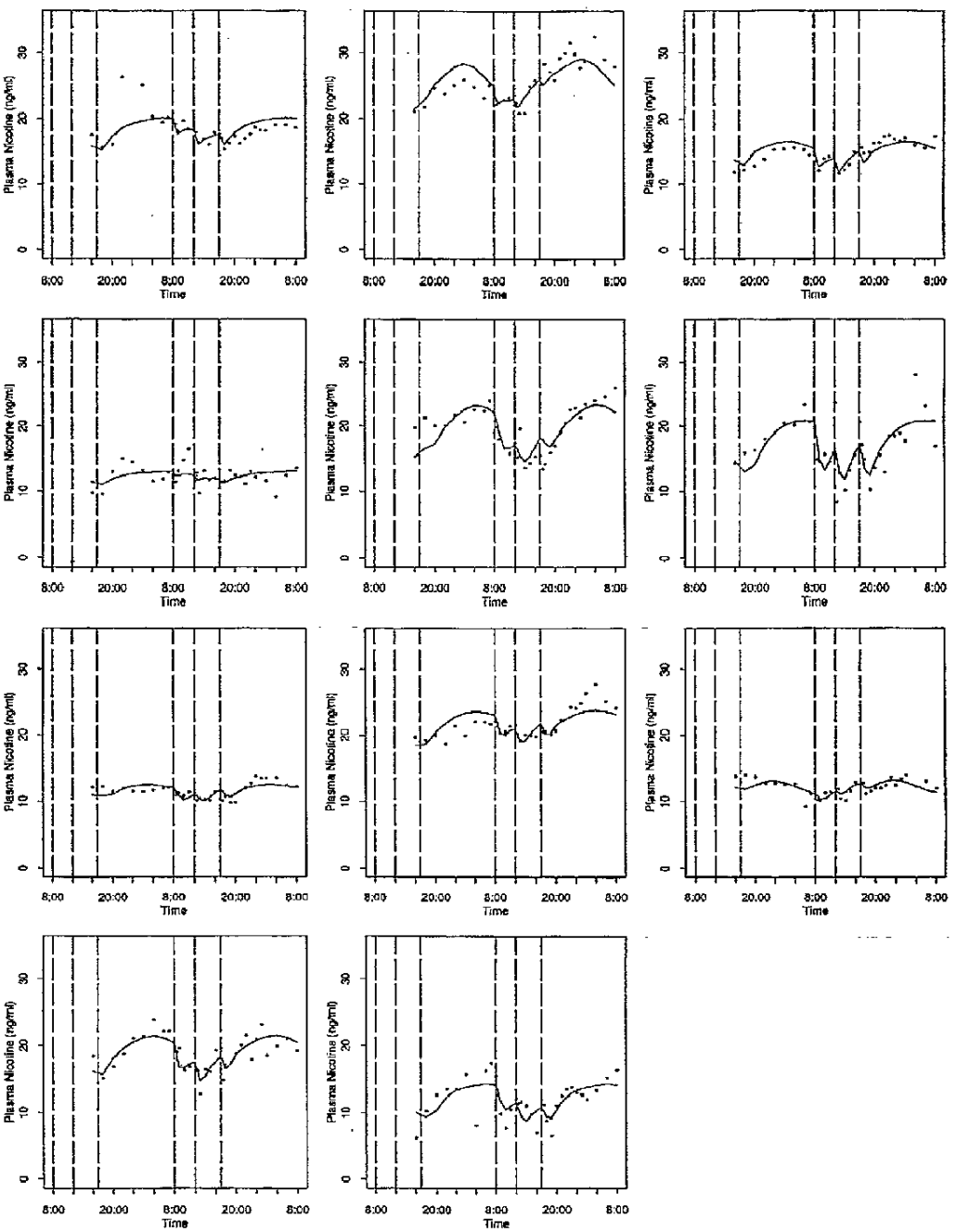


**Fig. 4.** Individuals' data and predictions of plasma concentration of nicotine versus clock time (individuals are ordered left to right, top to bottom). The *dots* are the observations, and the *solid lines* are the predictions obtained by semiparametric model.

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points is also an important and useful improvement. In this context it allows us to test the complexity of the circadian and meal effect components, fewer breakpoints being associated with lower complexity, without assuming a priori functional forms for these components.

The results obtained by the semiparametric and parametric approaches are similar with respect to the size of the meal effect and the extent of circadian variation. The semiparametric estimate indicates that the circadian variation is possibly more complex than a simple cosine function, obtaining a nonsymmetric function showing a flat region in clearance between 6 PM and 3 AM. The spline function used to represent the meal effect represents a slightly more realistic model than the parametric one, because it estimates a discrete end of the meal effect instead of an asymptotic attenuation. Individual estimates of the duration of meal effect are unrealistically long (see $T_{99,j}$, Table II). The parametric estimate shows a somewhat unrealistic sharpness in the meal effect, with a maximum reached at 10 minutes after the start of the meal. However, the sampling rate immediately after a meal is at most every half hour, which is insufficient to reach a definitive conclusion on the details of the shape of the meal effect.

In general we prefer the simplicity of representation offered by spline functions, their clean hierarchic framework (in terms of increasing number of breakpoints/parameters), and what we consider a vital safeguard in avoiding model misspecification (spline functions do not include any a priori knowledge and thus are influenced only by the data). Of course more complex (and realistic) parametric models can be used to represent clearance variation (for example, sums of cosine functions or sums of exponentials in equation 3), and such "parametric" models (we use quotes to stress their lack of physiological interpretability) can offer similar advantages.

We found that the average clearance of nicotine in this study over a 48-hour period was similar to that previously reported after a 30-minute infusion of nicotine.[2] The effects of meals on nicotine clearance as illustrated in Fig. 3 were substantial, with an average 42% increase in clearance peaking at approximately 1 hour after the beginning of the meal. The peak of clearance estimated by the parametric model occurs much sooner, and it is difficult to decide which estimate is the better one. Based on the semiparametric estimate the effect of meals lasted for approximately 3 hours. As a high-clearance drug the clearance of nicotine is expected to be influenced by liver blood flow, and this is presumed to be the basis for the effect of meals on the clearance of nicotine. Eating a meal produces an average 40% increase in liver blood flow,[14] similar in magnitude to the change in clearance of nicotine. The metabolism of other drugs has been shown to be increased by meals, although in no case has an estimate been made of the magnitude or duration of the change in drug clearance.

Table II. Individual parameter estimates (parametric model)

| *Subject No.* | $\gamma_{5,j}$ *(L/hr)* | $T_{max,j}$ *(hr)* | $M_{max,j}$ | $T_{99,j}$ *(hr)* | $\bar{A}_{min,j} = -A_{max,j}$ *(L/hr)* |
|---|---|---|---|---|---|
| 1 | 64.0* | 0.553 | 0.329 | 4.13 | −4.66 |
| 2 | 40.6 | 0.050 | 0.671* | 11.7 | −9.59 |
| 3 | 65.8 | 0.503 | 0.710 | 15.2 | −12.8 |
| 5 | 97.5 | 0.251 | 0.320 | 1.96 | −3.12 |
| 6 | 43.9 | 1.31 | 0.852 | 17.4 | −10.0 |
| 7 | 45.3 | 0.251* | 2.41 | 10.9 | −10.1 |
| 9 | 102 | 0.050 | 0.244 | 9.42* | −5.88* |
| 10 | 53.2 | 0.603 | 0.347 | 5.45 | −3.61 |
| 11 | 92.4 | 0.050 | 0.377 | 12.7 | −14.2 |
| 12 | 60.0 | 0.402 | 0.721 | 7.66 | −5.11 |
| 13 | 87.2 | 0.955 | 0.715 | 7.33 | −2.41 |
| Mean | 68.0 | 0.452 | 0.700 | 9.46 | −7.41 |
| SD | 22.7 | 0.398 | 0.606 | 4.72 | 4.09 |

*Median value for each parameter.

There was a significant circadian variation in nicotine clearance, but the magnitude of the circadian change in clearance (approximately 17% from peak to trough) was much smaller than the effect of meals on nicotine clearance. The times of day when peak and trough clearances were observed are of interest. The peak was seen at approximately 11:00 AM and the trough from 6 PM to 3 AM. As discussed previously the clearance of nicotine is likely to be influenced by liver blood flow. Circadian changes in liver blood flow measured as the clearance of indocyanine green have been reported.[7] Liver blood flow is highest at 8 AM and lowest in the late evening and early morning hours. Liver blood flow is also increased by physical activity, which is greater in the daytime compared with nighttime hours. Thus changes in liver blood flow can explain the circadian pattern of increased daytime and decreased nighttime clearance of nicotine and other high-clearance drugs such as midazolam,[15] bupivacaine,[4] and terbutaline.[16]

Also of note in our study was the considerable individual variability in the extent of meal-related

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and circadian changes in plasma nicotine levels (and therefore clearance) as shown in Fig. 4. Some subjects had quite substantial fluctuations in nicotine in association with meals and substantial day/night variation, whereas others had relatively flat curves. The reasons for individual variability in meal and circadian effects in nicotine clearance are not clear but might be related to individual differences in sleep/wake cycle, level of physical activity, or both.

Our findings have several potential biologic implications. Circadian changes in nicotine clearance could influence cigarette smoking behavior. Smokers typically smoke after meals, and a decline in plasma nicotine concentration caused by an increase in clearance could contribute to the urge to smoke. Some smokers smoke less in the evenings, and that behavior might be contributed to by the lower clearance in the evening compared with the morning. It was noted that there is considerable individual variability in the extent of circadian variation in nicotine clearance. Conceivably this could contribute to individual variability in temporal patterns of cigarette smoking.

Circadian changes in nicotine kinetics have implications in understanding blood nicotine concentrations during nicotine medication therapy, particularly with transdermal nicotine delivery systems. Pharmacokinetic analyses of nicotine absorption from nicotine patches have assumed a constant clearance of nicotine over a 24-hour period.[8] Because nicotine clearance is actually higher in the daytime and lower in the evening compared with the mean, the estimated release rates for nicotine from the patches are actually higher during the day and lower at night than originally reported.

Finally, that the clearance of nicotine is slower at night helps explain why significant plasma nicotine concentrations are seen in many smokers when they awake in the morning, even if they have not smoked during the night.[17] Persistence of nicotine levels in the body overnight may have implications in understanding tolerance to nicotine effects and potential nicotine-related toxicities.

In summary, we present a novel analytic approach for characterizing changes in drug clearance throughout the day. We find significant meal-related and circadian changes in nicotine clearance, which could be important in understanding the human pharmacologic characteristics of tobacco use and nicotine-containing medications.

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